

REMARKS

Claims 1-7, 10, 12 and 16 had been previously canceled. Claims 8 and 26 are canceled in this response.

Claims 9, 11, 13-15, 17-25 and 27-28 are currently pending. The dependency has been changed in claims 9, 11, 14, 15, 17 and 18.

Claims 9, 11, 13-15, 17-25 and 27-28 are currently amended. Support for “directly” can be found in the Specification as originally filed at page 13, line 1. Claim 18 also finds support in paragraphs [0020], [0037] and [0039]. Support for the amendments to claims 13, 17 and 25 can be found in previous claims 19 and 20.

New claims 29-32 have been added. Support for the new claim 29 can be found in paragraphs [0020], [0037] and [0039], while support for the remaining claims can be found in claims 13, 17 and 20.

No new matter has been added.

Statement of the Substance of an Interview

Interviews were held in the present application on December 6, 2010 and December 21, 2010, with Examiner Shin-Lin Chen and Applicants’ representative. Applicants’ representative sincerely thanks the Examiner for speaking with them. The substance of the Interview for the December 6, 2010 Interview accurately reflects the subject matter discussed on that date.

In the Interview conducted on December 21, 2010 the indefiniteness, double patenting, enablement, and obviousness rejections were discussed. With regard to the indefiniteness rejections, the Examiner confirmed that the change from “growth-factor” to “migration-enhancing factor” in claims 22-28 would overcome the indefiniteness rejection. With regard to the double-patenting rejection, Applicants’ representative pointed out the difference in scope between claims 14 and claims 20. The Examiner acknowledged that the double patenting rejection would be withdrawn. With regard to the enablement rejection, Applicants thank the Examiner for his comments in his Interview Summary. Specifically, the Examiner indicated that claims 13 and 17 would be enabled for PDGF-BB alone if the claims recited “directly administered to the injury site or the periphery thereof.” Applicants’ representative did not

understand the Examiner's statements to also require a specific type of administration of the MSCs for the claims to be enabled, especially in view of the discussion of claim 13.

With regard to the migration-enhancing factor, the Examiner maintained that only PDGF-BB was enabled. Applicants' representative disagreed, and pointed to the *in vitro* evidence in the Specification demonstrating that other migration-enhancing factors administered to the circulatory system would be expected to work.

Applicants' representative also spoke with the Examiner about the obviousness rejections of record. Applicants' representative pointed to Example 4 of the Specification, and to claim 17, where the MSCs are administered to the circulatory system and the migration enhancing factor is administered to the injury site. The Examiner acknowledged that claim 17 was unobvious.

While agreement with respect to all of the pending issues was not reached, Applicants sincerely thank the Examiner for his time and consideration of the present application.

Double Patenting

The Examiner has stated that if claim 14 is found allowable, claim 20 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

Applicants note that the scope of claims 14 and 20 is different. Specifically, claim 14 recites that the migration-enhancing factor be directly administered to the injured tissue or the periphery thereof. Claim 20 recites that the migration-enhancing factor is administered by injection directly into the injured tissue. Thus, the scope of claims 14 and 20 is different, and they are not substantial duplicates.

Claim Rejections – 35 USC § 112 – 2nd Paragraph

The Examiner has rejected claims 22-28 as indefinite for recitation of the phrase "in which the growth factor is PDGF-BB." Applicants have amended the claims, replacing "in which the growth factor is" with the phrase "in which the migration-enhancing factor is," thereby overcoming the rejection.

Claim Rejections – 35 USC § 112 – 1st Paragraph

The Examiner has rejected claims 8, 9, 11, 13-15 and 17-28 as lacking enablement. The Examiner acknowledges that the claims are enabled for localizing mesenchymal stem cells to an injury site in a patient by administering both mesenchymal stem cells and the recited migration-enhancing factor directly to the injury site. Applicants respectfully traverse.

As a preliminary matter, Applicants note that claim 8 has been canceled, thereby obviating the rejection for this claim.

The Examiner stated that the Specification does not reasonably provide enablement for localizing mesenchymal stem cells to an injury site by administering “migration-enhancing factor to the patient via various administration routes” (Office Action, page 3; see also page 5 second full paragraph). Applicants have amended claims 9, 11, 14 and 15 to depend from claim 13. Claim 13 has itself been amended by incorporating claim 8 to become independent and by reciting that the migration-enhancing factor is directly administered to the injured tissue. Claims 17, 19, 20, 21, and 25 are similarly amended. Applicants submit that this amendment obviates the Examiner’s concerns with regard to the administration route of the migration-enhancing factor.

The Examiner also suggests that the administration route of the mesenchymal stem cells would require undue experimentation to use (Office Action, page 3). However, the Examiner acknowledges that “GFP-MSCs injected through the tail vein of rats can migrate to the calves or migrate and accumulate in greater amounts at the site where PDGF-BB was localized (Example 4)” (Office Action, page 5). Applicants respectfully point out that claims 17, 19, 25 and their dependents all recite that the MSCs are administered to the circulatory system. Moreover, circulatory administration is more removed than direct administration to the injured tissue. Furthermore, alternative administration methods that would be realistically attempted by one of skill in the art are likely to be more specific than the systemic administration, which the Examiner already acknowledged to be effective. Accordingly, Applicants submit that the method of administration of the MSCs is fully enabled.

Finally, the Examiner suggests that of the specifically recited migration-enhancing factors, only PDGF-BB is enabled (Interview Summary of January 6, 2011). Applicants

respectfully disagree. The Examiner acknowledged that *in vitro* data was provided to demonstrate that the other migration-enhancing factors “enhance the migration and proliferation of the rabbit-derived mesenchymal stem cells *in vitro* (e.g., Examples 2-3)” (Office Action, page 5). Applicants submit that as a matter of law, Applicants are not required to provide *in vivo* results of efficacy.

Instead, Applicants need merely provide evidence which reasonably correlates the *in vitro* utility and the *in vivo* activity. See MPEP § 2164.02. Applicants herein provide evidence that the *in vitro* model tested in the Specification reasonably correlates to MSC migration activity *in vivo*.

Examples 2 and 3 of the Specification are performed with an art-recognized model of cell migration using a Boyden chamber (see page 19, line 7 of the Specification). The Boyden chamber model has been used to demonstrate cell migration and is known in the art to correlate to *in vivo* effects. Moreover the Specification itself demonstrates that PDGF-BB was effective to stimulate migration *in vitro* (see page 19, lines 14-17 and Fig. 1 A) and *in vivo* (see page 23, [0060] and Figs. 5 and 6).

Accordingly, Applicants submit that one of skill in the art would have understood that the *in vitro* evidence reasonably correlated to *in vivo* migration. Thus, they would have been able to use the full scope of the claimed methods without undue experimentation. Applicants therefore request that the rejection be withdrawn.

Claim Rejections – 35 USC § 103

The Examiner rejects claims 8, 9, 11, 13-15, 20-25, 27 and 28 under 35 U.S.C. § 103(a) as being unpatentable over each of Fiedler *et al.* (2002), Gerber *et al.* (U.S. 2002/0132978 A1), Badylak *et al.* (U.S. 6,375,989 B1), Desnoyers *et al.* (U.S. 7,456,262 B2), or Dabbagh *et al.* (1998). The Examiner also rejects claims 19 and 26 as being obvious over each of Fiedler, Gerber, Badylak, Desnoyers or Dabbagh in view of Sano *et al.* (2003).

Applicants respectfully traverse because the references either separately or as combined do not teach every feature of the claimed methods.

None of the cited references teaches administration of a mesenchymal stem cell migration-enhancing factor to an injured tissue for regeneration therapy and none of the cited references remotely suggests administration of both MSCs and the migration enhancing factor. The cited references are totally silent about enhancing the migration and accumulation of the administered MSCs in an injured tissue or suppressing the diffusion of the administered MSCs from an injured tissue by the administration of both MSCs and the migration enhancing factor to enhance regeneration of the injured tissue.

Moreover, the Examiner admits that the cited references “do not specifically teach administration of the PDGF-BB, HB-EFG, FGF-2 or HA to injured tissue for localizing mesenchymal stem cells to an injury site, or the mesenchymal stem cells and the migration enhancing factor are administered simultaneously, continuously or separately” (Office Action, page 10). Thus, not only do the references fail to teach administering MSCs (rather than simply using those already in the animal) the Examiner acknowledges that the method of administration of the migration enhancing factor is not taught either.

Instead the Examiner simply concludes that “it would be obvious for one of ordinary skill in the art to administer both mesenchymal stem cells and the migration-enhancing factor to the injury site or surrounding area to localize the mesenchymal stem cells to the injury site” (Office Action, page 11). However, Applicants submit that this conclusion is not legally sufficient under *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

A claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). There must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *Id.* Unless the combined prior art references suggest, either explicitly or implicitly the claimed invention, the Examiner must present a “*convincing line of reasoning* as to why one of ordinary skill in art would have found the claimed invention to have been obvious.” *Ex parte Rorher*, Appeal 2009-001292, 5 (BPAI, February 5, 2010) *citing Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (BPAI 1985)(emphasis added, internal quotations omitted).

Here, Applicants submit that the Examiner has provided no reason why one of skill in the art would have chosen to administer MSCs in addition to the migration-enhancing factor. In addition, there is no reason provided why one of skill in the art would expect that the administered MSCs would accumulate in the injured tissue or that the administration of the migration-enhancing factor would then suppress the diffusion of the administered MSCs from the injured tissue site. Accordingly, Applicants submit that the present invention demonstrates unexpected results as well. For at least these reasons, Applicants request that the rejection be withdrawn.

Applicants note that the Examiner has not rejected claims 17 and 18 as obvious. Claim 17 recites that the MSCs are administered to the circulatory system and that the migration-enhancing factor is directly injected. Claim 18 recites that the MSCs are administered to the injured tissue or its periphery, before, during or after injection of the migration enhancing factor. Applicants submit that these claims are not obvious and thank the Examiner for his recognition of the novel and unobvious features of the claimed method.

CONCLUSION

In view of the above remarks, all of the claims are submitted as defining clear, enabled, and non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested. Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D., Reg. No. 47,604 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petitions for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of \$245.00 is attached hereto.

Application No. 10/594,595
Amendment dated April 12, 2011
Reply to Office Action of November 12, 2010

Docket No.: 0230-0242PUS1

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: April 12, 2011

Respectfully submitted,

By:  _____

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